DETAILED ACTION

Applicant's amendment filed 4-12-11 has been entered. Claims 9, 11, 13-15, 17-25, 27 and 28 have been amended. Claims 8 and 26 have been canceled. Claims 29-32 have been added. Claims 9, 11, 13-15, 17-25 and 27-32 are pending and under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 9, 11, 13-15, 17, 20, 21, 23, 24, 27 and 28 remain rejected and newly added claims 29-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for localizing mesenchymal stem cells to an injury site in a patient by administering both mesenchymal stem cells and the recited migration-enhancing factor directly to the injury site or by administering mesenchymal stem cell via circulatory system and administering PDGF-BB directly to injury site, does not reasonably provide enablement for localizing mesenchymal stem cells to an injury site in a patient by administering mesenchymal stem cells via various administration routes and administering the recited migration-enhancing factor to the patient directly to the injury site. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims and is repeated for the reasons set forth in the preceding Official action mailed 11-12-10. Applicant's arguments filed 4-12-11 have been fully considered but they are not persuasive.

Applicant argues that claims 17, 19, 25 and their dependent claims all recite that the MSCs are administered to the circulatory system, which is more removed than direct administration to the injury tissue. One of skilled in the art would try more specific route than the systemic administration and those routes are enabled. Applicant argues that the in vitro data of migration-enhancing factors other than PDGF-BB have been provided, there is no need to provide in vivo results of efficacy. Examples 2 and 3 of the specification use Boyden chamber to demonstrate cell migration in vitro and it is known in the art to correlate to in vivo effects (amendment, p. 9-10). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 11-12-10.

The claims read on administering mesenchymal stem cells to a patient via various administration routes such that the mesenchymal stem cells are localized to an injury site in said patient. The delivery of mesenchymal stem cells to an injury site via various administration routes would encounter various barriers in vivo, such as cell membranes and tight junctions between adjacent epithelial cells, mucus layer and efflux system, enzymatic barrier, fast elimination from the systemic circulation, the potential to develop an immune response, uptake by non-target tissues, and inefficient target cell entry. The in vitro data of enhancing migration and accumulation of MSCs by the recited migration-enhancing factors cannot be extrapolated into in vivo success of attracting MSCs to various injury sites in a subject. There is no evidence of record that demonstrates administration of the mesenchymal stem cells via various administration routes would be able to localize the mesenchymal stem cells to a target injury site in vivo. There is also no evidence of record that shows the migration-enhancing factors other

than PDGF-BB, administered directly to the injury site, can localize the MSCs administered via circulatory system to the injury site.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 9, 11, 13-15, 20, 21, 23, 24, 27 and 28 remain rejected, the amended claim 18, and newly added claims 29, 30 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over each of Fiedler et al., 2002 (Journal of Cellular Biochemistry, Vol. 87, p. 305-312), Gerber et al., 2002 (US 20020132978 A1), Badylak et al., 2002 (US Patent No. 6,375,989 B1), Desnoyers et al., 2008 (US Patent No. 7,456,262 B2), or Dabbagh et al., 1998 (Thrombosis and Haemostasis, Vol. 79, No. 2, pp. 405, Summary only) and is repeated for the reasons set forth in

the preceding Official action mailed 11-12-10. Applicant's arguments filed 4-12-11 have been fully considered but they are not persuasive.

Applicant argues that none of the cited references teaches administration of a mesenchymal stem cell migration-enhancing factor to an injured tissue and none of the cited references remotely suggests administration of both mesenchymal stem cells and migration enhancing factor. There must be a reason to prompt one of ordinary skill to combine the elements in the way the claimed invention does. There is no motivation to combine the cited references to administer MSCs in addition to the migration-enhancing factor. There is no reason to expect that the administered MSCs would accumulate in the injured tissue or the administered migration-enhancing factor would suppress the diffusion of the administered MSCs (amendment, p. 11-12). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 11-12-10.

The importance of mesenchymal stem cells or mesenchymal progenitor cells in tissue regeneration was well known in the art. For example, the cited reference Fiedler teaches that "for bone development, remodeling, and repair; the recruitment of mesenchymal progenitor cells (MPC) and their differentiation to osteoblasts is mandatory" (e.g. Abstract). Fiedler teaches that rhPDGF-bb can stimulate migration of primary human mesenchymal progenitor cells (MPC) in a dose-dependent manner, Gerber teaches HB-EGF stimulates mesenchymal cell proliferation and migration and promotes renal epithelial cell survival, Badylak teaches FGF-2 promotes mesenchymal cell migration and proliferation to accelerate healing of gastric mucosa and calvarian bone, Desnoyers teaches that hyaluronic acid (HA) facilitates cell migration during wound healing, and Dabbagh teaches that thrombin can stimulate mesenchymal cell migration

and proliferation. Since rhPDGF-bb, HB-EGF, FGF-2, HA and thrombin can stimulate cell migration and proliferation of mesenchymal cells and the recruitment of mesenchymal progenitor cells is important in tissue regeneration, one of ordinary skill in the art would have been motivated to administer both the MSCs and migration-enhancing factors directly to the injury site so as to promote tissue regeneration. There would be reasonable expectation of success that the administered migration-enhancing factors can enhance the migration and accumulation of the administered MSCs in injured tissue or suppress the diffusion of the administered MSCs from the injured tissue because those migration-enhancing factors are known to attract the MSCs.

Double Patenting

Applicant is advised that should claim 22 be found allowable, claim 25 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Applicant's amendment filed 4-12-11 necessitates this new ground of objection.

Conclusion

Claims 9, 11, 13-15, 17, 18, 20, 21, 23, 24 and 27-32 are rejected. Claims 19 and 22 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in

independent form including all of the limitations of the base claim and any intervening claims. Claim 25 is objected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Shin-Lin Chen/
Primary Examiner
Art Unit 1632